



SEQUENCE LISTING

<110> Wyeth
Wolfman, Neil

<120> MODIFIED AND STABILIZED GDF PROPEPTIDES AND USES THEREOF

<130> 08702.0100-00000

<150> 10/071,499

<151> 2002-02-08

<150> 60/257,509

<151> 2001-02-08

<160> 23

<170> PatentIn version 3.1

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<210> 1

<211> 375

<212> PRT

<213> Homo sapiens

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Val Glu Lys Glu Gly Leu Cys Asn Ala Cys Thr Trp Arg Gln Asn Thr
35 40 45

Lys Ser Ser Arg Ile Glu Ala Ile Lys Ile Gln Ile Leu Ser Lys Leu
50 55 60

Arg Leu Glu Thr Ala Pro Asn Ile Ser Lys Asp Val Ile Arg Gln Leu
65 70 75 80

Leu Pro Lys Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr Asp Val
85 90 95

Gln Arg Asp Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr His
100 105 110

Ala Thr Thr Glu Thr Ile Ile Thr Met Pro Thr Glu Ser Asp Phe Leu
115 120 125

Met Gln Val Asp Gly Lys Pro Lys Cys Cys Phe Phe Lys Phe Ser Ser
 130 135 140

Lys Ile Gln Tyr Asn Lys Val Val Lys Ala Gln Leu Trp Ile Tyr Leu
 145 150 155 160

Arg Pro Val Glu Thr Pro Thr Thr Val Phe Val Gln Ile Leu Arg Leu
 165 170 175

Ile Lys Pro Met Lys Asp Gly Thr Arg Tyr Thr Gly Ile Arg Ser Leu
 180 185 190

Lys Leu Asp Met Asn Pro Gly Thr Gly Ile Trp Gln Ser Ile Asp Val
 195 200 205

Lys Thr Val Leu Gln Asn Trp Leu Lys Gln Pro Glu Ser Asn Leu Gly
 210 215 220

Ile Glu Ile Lys Ala Leu Asp Glu Asn Gly His Asp Leu Ala Val Thr
 225 230 235 240

Phe Pro Gly Pro Gly Glu Asp Gly Leu Asn Pro Phe Leu Glu Val Lys
 245 250 255

Val Thr Asp Thr Pro Lys Arg Ser Arg Arg Asp Phe Gly Leu Asp Cys
 260 265 270

Asp Glu His Ser Thr Glu Ser Arg Cys Cys Arg Tyr Pro Leu Thr Val
 275 280 285

Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg Tyr
 290 295 300

Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu Phe Val Phe Leu Gln Lys
 305 310 315 320

Tyr Pro His Thr His Leu Val His Gln Ala Asn Pro Arg Gly Ser Ala
 325 330 335

Gly Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met Leu Tyr
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Val Asp Arg Cys Gly Cys Ser
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 120

gcatgtactt ggagacaaaa cactaaatct tcaagaatag aagccattaa gatacaaatc
 180

ctcagtaaac ttcgtctgga aacagctcct aacatcagca aagatgttat aagacaactt
 240

ttacccaaag ctctccact ccgggaactg attgatcagt atgatgtcca gagggatgac
 300

agcagcgatg gctcttttga agatgacgat tatcacgcta caacggaaac aatcattacc
 360

atgcctacag agtctgattt tctaatacaa gtggatggaa aacccaaatg ttgcttcttt
 420

aaatttagct ctaaaataca atacaataaa gtagtaaagg cccaactatg gatatatattg
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agacccgtcg agactcctac aacagtgttt gtgcaaatcc tgagactcat caaacctatg
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aaagacggta caaggtatac tggaaatcga tctctgaaac ttgacatgaa cccaggcact
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900

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960

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1020

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<213> Homo sapiens

<400> 3

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Arg Tyr Pro Leu Thr Val Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile
20 25 30

Ile Ala Pro Lys Arg Tyr Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu
35 40 45

Phe Val Phe Leu Gln Lys Tyr Pro His Thr His Leu Val His Gln Ala
50 55 60

Asn Pro Arg Gly Ser Ala Gly Pro Cys Cys Thr Pro Thr Lys Met Ser
65 70 75 80

Pro Ile Asn Met Leu Tyr Phe Asn Gly Lys Glu Gln Ile Ile Tyr Gly
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Lys Ile Pro Ala Met Val Val Asp Arg Cys Gly Cys Ser
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120

aattactgct ctggagagtg tgaatttgta tttttacaaa aatatacctca tactcatctg
180

gtacaccaag caaacccag aggttcagca ggcccttgct gtactccac aaagatgtct
240

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<210> 5
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<212> PRT
<213> Homo sapiens

<400> 5

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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Glu | Asn | Ser | Glu | Gln | Lys | Glu | Asn | Val | Glu | Lys | Glu | Gly | Leu | Cys |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Ala | Cys | Thr | Trp | Arg | Gln | Asn | Thr | Lys | Ser | Ser | Arg | Ile | Glu | Ala |
| | | | 20 | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Lys | Ile | Gln | Ile | Leu | Ser | Lys | Leu | Arg | Leu | Glu | Thr | Ala | Pro | Asn |
| | | 35 | | | | | 40 | | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Ser | Lys | Asp | Val | Ile | Arg | Gln | Leu | Leu | Pro | Lys | Ala | Pro | Pro | Leu |
| | 50 | | | | | 55 | | | | | 60 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Glu | Leu | Ile | Asp | Gln | Tyr | Asp | Val | Gln | Arg | Asp | Asp | Ser | Ser | Asp |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Ser | Leu | Glu | Asp | Asp | Asp | Tyr | His | Ala | Thr | Thr | Glu | Thr | Ile | Ile |
| | | | | 85 | | | | | 90 | | | | | 95 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Met | Pro | Thr | Glu | Ser | Asp | Phe | Leu | Met | Gln | Val | Asp | Gly | Lys | Pro |
| | | | 100 | | | | | 105 | | | | | 110 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Cys | Cys | Phe | Phe | Lys | Phe | Ser | Ser | Lys | Ile | Gln | Tyr | Asn | Lys | Val |
| | | 115 | | | | | 120 | | | | | 125 | | | |

Val Lys Ala Gln Leu Trp Ile Tyr Leu Arg Pro Val Glu Thr Pro Thr
 130 135 140

Thr Val Phe Val Gln Ile Leu Arg Leu Ile Lys Pro Met Lys Asp Gly
 145 150 155 160

Thr Arg Tyr Thr Gly Ile Arg Ser Leu Lys Leu Asp Met Asn Pro Gly
 165 170 175

Thr Gly Ile Trp Gln Ser Ile Asp Val Lys Thr Val Leu Gln Asn Trp
 180 185 190

Leu Lys Gln Pro Glu Ser Asn Leu Gly Ile Glu Ile Lys Ala Leu Asp
 195 200 205

Glu Asn Gly His Asp Leu Ala Val Thr Phe Pro Gly Pro Gly Glu Asp
 210 215 220

Gly Leu Asn Pro Phe Leu Glu Val Lys Val Thr Asp Thr Pro Lys Arg
 225 230 235 240

Ser Arg Arg

<210> 6
 <211> 729
 <212> DNA
 <213> Homo sapiens

<400> 6
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tggagacaaa acactaaatc ttcaagaata gaagccatta agatacaaat cctcagtaaa
 120

cttcgtcttg aaacagctcc taacatcagc aaagatgtta taagacaact ttaccctaaa
 180

gctcctccac tccgggaact gattgatcag tatgatgtcc agagggatga cagcagcgat
 240

ggctcttttg aagatgacga ttatcacgct acaacggaaa caatcattac catgcctaca
 300

gagtctgatt ttctaatagca agtggatgga aaacccaaat gttgcttctt taaatttagc
 360

tctaaaatac aatacaataa agtagtaaag gcccaactat ggatatattt gagaccgctc
420

gagactccta caacagtgtt tgtgcaaatac ctgagactca tcaaacttat gaaagacggt
480

acaaggtata ctggaatccg atctctgaaa cttgacatga acccaggcac tggatatttg
540

cagagcattg atgtgaagac agtgttgcaa aattggctca aacaacctga atccaactta
600

ggcattgaaa taaaagcttt agatgagaat ggcatgatc ttgctgtaac cttcccagga
660

ccaggagaag atgggctgaa tccgttttta gaggtcaagg taacagacac accaaaaaga
720

tccagaagg
729

<210> 7
<211> 407
<212> PRT
<213> Homo sapiens

<400> 7

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Val | Leu | Ala | Ala | Pro | Leu | Leu | Leu | Gly | Phe | Leu | Leu | Leu | Ala | Leu |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Leu | Arg | Pro | Arg | Gly | Glu | Ala | Ala | Glu | Gly | Pro | Ala | Ala | Ala | Ala |
| | | | 20 | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Ala | Ala | Ala | Ala | Ala | Ala | Ala | Ala | Gly | Val | Gly | Gly | Glu | Arg | Ser |
| | | 35 | | | | | | 40 | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Arg | Pro | Ala | Pro | Ser | Val | Ala | Pro | Glu | Pro | Asp | Gly | Cys | Pro | Val |
| | 50 | | | | | 55 | | | | | 60 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | Val | Trp | Arg | Gln | His | Ser | Arg | Glu | Leu | Arg | Leu | Glu | Ser | Ile | Lys |
| 65 | | | | | 70 | | | | | 75 | | | | 80 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Gln | Ile | Leu | Ser | Lys | Leu | Arg | Leu | Lys | Glu | Ala | Pro | Asn | Ile | Ser |
| | | | | 85 | | | | | 90 | | | | | 95 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Glu | Val | Val | Lys | Gln | Leu | Leu | Pro | Lys | Ala | Pro | Pro | Leu | Gln | Gln |
| | | | 100 | | | | | | 105 | | | | | 110 | |

Ile Leu Asp Leu His Asp Phe Gln Gly Asp Ala Leu Gln Pro Glu Asp
115 120 125

Phe Leu Glu Glu Asp Glu Tyr His Ala Thr Thr Glu Thr Val Ile Ser
130 135 140

Met Ala Gln Glu Thr Asp Pro Ala Val Gln Thr Asp Gly Ser Pro Leu
145 150 155 160

Cys Cys His Phe His Phe Ser Pro Lys Val Met Phe Thr Lys Val Leu
165 170 175

Lys Ala Gln Leu Trp Val Tyr Leu Arg Pro Val Pro Arg Pro Ala Thr
180 185 190

Val Tyr Leu Gln Ile Leu Arg Leu Lys Pro Leu Thr Gly Glu Gly Thr
195 200 205

Ala Gly Gly Gly Gly Gly Gly Arg Arg His Ile Arg Ile Arg Ser Leu
210 215 220

Lys Ile Glu Leu His Ser Arg Ser Gly His Trp Gln Ser Ile Asp Phe
225 230 235 240

Lys Gln Val Leu His Ser Trp Phe Arg Gln Pro Gln Ser Asn Trp Gly
245 250 255

Ile Glu Ile Asn Ala Phe Asp Pro Ser Gly Thr Asp Leu Ala Val Thr
260 265 270

Ser Leu Gly Pro Gly Ala Glu Gly Leu His Pro Phe Met Glu Leu Arg
275 280 285

Val Leu Glu Asn Thr Lys Arg Ser Arg Arg Asn Leu Gly Leu Asp Cys
290 295 300

Asp Glu His Ser Ser Glu Ser Arg Cys Cys Arg Tyr Pro Leu Thr Val
305 310 315 320

Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg Tyr
325 330 335

Lys Ala Asn Tyr Cys Ser Gly Gln Cys Glu Tyr Met Phe Met Gln Lys
340 345 350

Tyr Pro His Thr His Leu Val Gln Gln Ala Asn Pro Arg Gly Ser Ala
355 360 365

Gly Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met Leu Tyr
370 375 380

Phe Asn Asp Lys Gln Gln Ile Ile Tyr Gly Lys Ile Pro Gly Met Val
385 390 395 400

Val Asp Arg Cys Gly Cys Ser
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<210> 8
<211> 1221
<212> DNA
<213> Homo sapiens

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120

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180

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240

tcgcagatct tgagcaaact gcggctcaag gaggcgcca acatcagccg cgagggtggtg
300

aagcagctgc tgcccaaggc gccgccgctg cagcagatcc tggacctaca cgacttccag
360

ggcgacgcgc tgcagcccga ggacttcctg gaggaggacg agtaccacgc caccaccgag
420

accgtcatta gcatggccca ggagacggac ccagcagtac agacagatgg cagccctctc
480

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540

tgggtgtacc tacggcctgt accccgcca gccacagtct acctgcagat cttgcgacta
600

aaacccctaa ctggggaagg gaccgcaggg ggagggggcg gaggccggcg tcacatccgt
660

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720

aagcaagtgc tacacagctg gttccgccag ccacagagca actggggcat cgagatcaac
780

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840

ctgcatccat tcatggagct tcgagtccta gagaacacaa aacgttcccg gcggaacctg
900

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960

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1020

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1080

caggccaatc caagaggctc tgctggggccc tgttgtaccc ccaccaagat gtccccaatc
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1200

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1221

<210> 9
<211> 109
<212> PRT
<213> Homo sapiens

<400> 9

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Leu | Gly | Leu | Asp | Cys | Asp | Glu | His | Ser | Ser | Glu | Ser | Arg | Cys | Cys |
| 1 | | | 5 | | | | | 10 | | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Tyr | Pro | Leu | Thr | Val | Asp | Phe | Glu | Ala | Phe | Gly | Trp | Asp | Trp | Ile |
| | | | 20 | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Ala | Pro | Lys | Arg | Tyr | Lys | Ala | Asn | Tyr | Cys | Ser | Gly | Gln | Cys | Glu |
| | 35 | | | | | | 40 | | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Met | Phe | Met | Gln | Lys | Tyr | Pro | His | Thr | His | Leu | Val | Gln | Gln | Ala |
| 50 | | | | | | 55 | | | | | 60 | | | | |

Asn Pro Arg Gly Ser Ala Gly Pro Cys Cys Thr Pro Thr Lys Met Ser
65 70 75 80

Pro Ile Asn Met Leu Tyr Phe Asn Asp Lys Gln Gln Ile Ile Tyr Gly
85 90 95

Lys Ile Pro Gly Met Val Val Asp Arg Cys Gly Cys Ser
100 105

<210> 10
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<212> DNA
<213> Homo sapiens

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acagtggact ttgaggcttt cggctgggac tggatcatcg cacctaagcg ctacaaggcc
120

aactactgct cgggccagtg cgagtacatg ttcattgcaaa aatatccgca taccatttg
180

gtgcagcagg ccaatccaag aggctctgct gggccctggt gtacccccac caagatgtcc
240

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300

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327

<210> 11
<211> 274
<212> PRT
<213> Homo sapiens

<400> 11

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Ala Gly Val Gly Gly Glu Arg Ser Ser Arg Pro Ala Pro Ser Val Ala
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Pro Glu Pro Asp Gly Cys Pro Val Cys Val Trp Arg Gln His Ser Arg
35 40 45

Glu Leu Arg Leu Glu Ser Ile Lys Ser Gln Ile Leu Ser Lys Leu Arg
 50 55 60

Leu Lys Glu Ala Pro Asn Ile Ser Arg Glu Val Val Lys Gln Leu Leu
 65 70 75 80

Pro Lys Ala Pro Pro Leu Gln Gln Ile Leu Asp Leu His Asp Phe Gln
 85 90 95

Gly Asp Ala Leu Gln Pro Glu Asp Phe Leu Glu Glu Asp Glu Tyr His
 100 105 110

Ala Thr Thr Glu Thr Val Ile Ser Met Ala Gln Glu Thr Asp Pro Ala
 115 120 125

Val Gln Thr Asp Gly Ser Pro Leu Cys Cys His Phe His Phe Ser Pro
 130 135 140

Lys Val Met Phe Thr Lys Val Leu Lys Ala Gln Leu Trp Val Tyr Leu
 145 150 155 160

Arg Pro Val Pro Arg Pro Ala Thr Val Tyr Leu Gln Ile Leu Arg Leu
 165 170 175

Lys Pro Leu Thr Gly Glu Gly Thr Ala Gly Gly Gly Gly Gly Gly Arg
 180 185 190

Arg His Ile Arg Ile Arg Ser Leu Lys Ile Glu Leu His Ser Arg Ser
 195 200 205

Gly His Trp Gln Ser Ile Asp Phe Lys Gln Val Leu His Ser Trp Phe
 210 215 220

Arg Gln Pro Gln Ser Asn Trp Gly Ile Glu Ile Asn Ala Phe Asp Pro
 225 230 235 240

Ser Gly Thr Asp Leu Ala Val Thr Ser Leu Gly Pro Gly Ala Glu Gly
 245 250 255

Leu His Pro Phe Met Glu Leu Arg Val Leu Glu Asn Thr Lys Arg Ser
 260 265 270

Arg Arg

<210> 12
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<212> DNA
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120
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660
cacagctggg tccgccagcc acagagcaac tggggcatcg agatcaacgc ctttgatccc
720
agtggcacag acctggctgt cacctccctg gggccgggag ccgaggggct gcatccattc
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822

<210> 13
<211> 23
<212> PRT
<213> Homo sapiens

<400> 13

Met Gln Lys Leu Gln Leu Cys Val Tyr Ile Tyr Leu Phe Met Leu Ile
1 5 10 15

Val Ala Gly Pro Val Asp Leu
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<210> 14

<211> 24

<212> PRT

<213> Homo sapiens

<400> 14

Met Val Leu Ala Ala Pro Leu Leu Leu Gly Phe Leu Leu Leu Ala Leu
1 5 10 15

Glu Leu Arg Pro Arg Gly Glu Ala
20

<210> 15

<211> 232

<212> PRT

<213> Homo sapiens

<400> 15

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1 5 10 15

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
20 25 30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
35 40 45

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
50 55 60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65 70 75 80

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
85 90 95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
 100 105 110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
 115 120 125

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
 130 135 140

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
 145 150 155 160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
 165 170 175

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
 180 185 190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
 195 200 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
 210 215 220

Ser Leu Ser Leu Ser Pro Gly Lys
 225 230

<210> 16
 <211> 227
 <212> PRT
 <213> Homo sapiens

<400> 16

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Leu Gly
 1 5 10 15

Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
 20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
 35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
 50 55 60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
100 105 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115 120 125

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
130 135 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145 150 155 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
165 170 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
180 185 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
195 200 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
210 215 220

Pro Gly Lys
225

<210> 17
<211> 4
<212> PRT
<213> Homo sapiens

<400> 17

Gly Ser Gly Ser
1

<210> 18
 <211> 4
 <212> PRT
 <213> Human

<400> 18

Arg Ser Arg Arg
 1

<210> 19
 <211> 7
 <212> PRT
 <213> Human

<400> 19

Ala Glu Gly Pro Ala Ala Ala
 1 5

<210> 20
 <211> 498
 <212> PRT
 <213> chimera

<400> 20

Met Met Gln Lys Leu Gln Met Tyr Val Tyr Ile Tyr Leu Phe Met Leu
 1 5 10 15

Ile Ala Ala Gly Pro Val Asp Leu Asn Glu Gly Ser Glu Arg Glu Glu
 20 25 30

Asn Val Glu Lys Glu Gly Leu Cys Asn Ala Cys Ala Trp Arg Gln Asn
 35 40 45

Thr Arg Tyr Ser Arg Ile Glu Ala Ile Lys Ile Gln Ile Leu Ser Lys
 50 55 60

Leu Arg Leu Glu Thr Ala Pro Asn Ile Ser Lys Asp Ala Ile Arg Gln
 65 70 75 80

Leu Leu Pro Arg Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr Asp
 85 90 95

Val Gln Arg Asp Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr
 100 105 110

His Ala Thr Thr Glu Thr Ile Ile Thr Met Pro Thr Glu Ser Asp Phe
 115 120 125

Leu Met Gln Ala Asp Gly Lys Pro Lys Cys Cys Phe Phe Lys Phe Ser
 130 135 140

Ser Lys Ile Gln Tyr Asn Lys Val Val Lys Ala Gln Leu Trp Ile Tyr
 145 150 155 160

Leu Arg Pro Val Lys Thr Pro Thr Thr Val Phe Val Gln Ile Leu Arg
 165 170 175

Leu Ile Lys Pro Met Lys Asp Gly Thr Arg Tyr Thr Gly Ile Arg Ser
 180 185 190

Leu Lys Leu Asp Met Ser Pro Gly Thr Gly Ile Trp Gln Ser Ile Asp
 195 200 205

Val Lys Thr Val Leu Gln Asn Trp Leu Lys Gln Pro Glu Ser Asn Leu
 210 215 220

Gly Ile Glu Ile Lys Ala Leu Asp Glu Asn Gly His Asp Leu Ala Val
 225 230 235 240

Thr Phe Pro Gly Pro Gly Glu Asp Gly Leu Asn Pro Phe Leu Glu Val
 245 250 255

Lys Val Thr Asp Thr Pro Lys Arg Ser Glu Pro Arg Gly Pro Thr Ile
 260 265 270

Lys Pro Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Glu Gly Gly
 275 280 285

Pro Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile
 290 295 300

Ser Leu Ser Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp
 305 310 315 320

Asp Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His
 325 330 335

Thr Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg
 340 345 350

Val Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys
 355 360 365

Ala Phe Ala Cys Ala Val Asn Asn Lys Asp Leu Pro Ala Pro Ile Glu
 370 375 380

Arg Thr Ile Ser Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr
 385 390 395 400

Val Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu
 405 410 415

Thr Cys Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp
 420 425 430

Thr Asn Asn Gly Lys Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val
 435 440 445

Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu
 450 455 460

Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His
 465 470 475 480

Glu Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro
 485 490 495

Gly Lys

<210> 21
 <211> 496
 <212> PRT
 <213> chimera

<400> 21

Met Met Gln Lys Leu Gln Phe Ile Tyr Val Tyr Ile Tyr Leu Phe Asn
 1 5 10 15

Leu Ile Ala Ala Gly Pro Val Asp Leu Asn Asn Ile Glu Gly Ser Glu
 20 25 30

Arg Glu Glu Asn Val Glu Lys Glu Gly Leu Cys Asn Ala Cys Ala Trp
 35 40 45

Arg Gln Asn Thr Arg Tyr Ser Arg Ile Glu Ala Ile Lys Ile Gln Ile
 50 55 60

Leu Ser Lys Leu Arg Leu Glu Thr Ala Pro Ile Asn Ile Ser Lys Asp
 65 70 75 80

Ala Ile Arg Gln Leu Leu Pro Arg Ala Pro Pro Leu Arg Glu Leu Ile
 85 90 95

Asp Gln Tyr Asp Val Gln Arg Asp Asp Ser Ser Asp Gly Ser Leu Glu
 100 105 110

Asp Asp Asp Tyr His Ala Thr Thr Glu Thr Ile Ile Thr Met Pro Thr
 115 120 125

Glu Ser Asp Phe Leu Met Gln Ala Asp Gly Lys Pro Lys Cys Cys Phe
 130 135 140

Phe Lys Phe Ser Ser Lys Ile Gln Tyr Asn Asn Asn Lys Val Val Lys
 145 150 155 160

Ala Gln Leu Trp Ile Tyr Leu Arg Pro Val Lys Thr Pro Thr Thr Val
 165 170 175

Phe Val Gln Ile Leu Arg Leu Ile Lys Pro Met Lys Asp Gly Thr Arg
 180 185 190

Tyr Thr Gly Ile Arg Ser Leu Lys Leu Asp Met Ser Pro Gly Thr Gly
 195 200 205

Ile Trp Gln Ser Ile Asp Val Lys Thr Val Leu Gln Asn Trp Leu Lys
 210 215 220

Gln Pro Glu Ser Asn Leu Gly Ile Glu Ile Lys Ala Leu Asp Glu Asn
 225 230 235 240

Gly His Asp Leu Ala Val Thr Phe Pro Gly Pro Gly Glu Asp Gly Leu
 245 250 255

Asn Pro Phe Leu Glu Val Lys Val Thr Asp Thr Pro Lys Arg Ser Gly
 260 265 270

Ser Gly Ser Glu Pro Arg Gly Pro Thr Ile Lys Pro Cys Pro Pro Cys
 275 280 285

Lys Cys Pro Ala Pro Asn Leu Glu Gly Gly Pro Ser Val Phe Ile Phe
 290 295 300

Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro Ile Val
 305 310 315 320

Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln Ile
 325 330 335

Ser Val His Thr Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser
 340 345 350

Thr Leu Arg Val Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met
 355 360 365

Ser Gly Lys Ala Phe Ala Cys Ala Val Asn Asn Lys Asp Leu Pro Ala
 370 375 380

Pro Ile Glu Arg Thr Ile Ser Lys Pro Lys Gly Ser Val Arg Ala Pro
 385 390 395 400

Gln Val Tyr Val Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln
 405 410 415

Val Thr Leu Thr Cys Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr
 420 425 430

Val Glu Trp Thr Asn Asn Gly Lys Thr Glu Leu Asn Tyr Lys Asn Thr
 435 440 445

Glu Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu
 450 455 460

Arg Val Glu Lys Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu Gly
 465 470 475 480

Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly Lys
485 490 495

<210> 22
<211> 497
<212> PRT
<213> chimera

<400> 22

Met Met Gln Lys Leu Gln Leu Cys Val Tyr Ile Tyr Leu Phe Met Leu
1 5 10 15

Ile Val Ala Gly Pro Val Asp Leu Asn Glu Asn Ser Glu Gln Lys Glu
20 25 30

Asn Val Glu Lys Glu Gly Leu Cys Asn Ala Cys Thr Trp Arg Gln Asn
35 40 45

Thr Lys Ser Ser Arg Ile Glu Ala Ile Lys Ile Gln Ile Leu Ser Lys
50 55 60

Leu Arg Leu Glu Thr Ala Pro Asn Ile Ser Lys Asp Val Ile Arg Gln
65 70 75 80

Leu Leu Pro Lys Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr Asp
85 90 95

Val Gln Arg Asp Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr
100 105 110

His Ala Thr Thr Glu Thr Ile Ile Thr Met Pro Thr Glu Ser Asp Phe
115 120 125

Leu Met Gln Val Asp Gly Lys Pro Lys Cys Cys Phe Phe Lys Phe Ser
130 135 140

Ser Lys Ile Gln Tyr Asn Lys Val Val Lys Ala Gln Leu Trp Ile Tyr
145 150 155 160

Leu Arg Pro Val Glu Thr Pro Thr Thr Val Phe Val Gln Ile Leu Arg
165 170 175

Leu Ile Lys Pro Met Lys Asp Gly Thr Arg Tyr Thr Gly Ile Arg Ser
180 185 190

Leu Lys Leu Asp Met Asn Pro Gly Thr Gly Ile Trp Gln Ser Ile Asp
 195 200 205

Val Lys Thr Val Leu Gln Asn Trp Leu Lys Gln Pro Glu Ser Asn Leu
 210 215 220

Gly Ile Glu Ile Lys Ala Leu Asp Glu Asn Gly His Asp Leu Ala Val
 225 230 235 240

Thr Phe Pro Gly Pro Gly Glu Asp Gly Leu Asn Pro Phe Leu Glu Val
 245 250 255

Lys Val Thr Asp Thr Pro Lys Arg Ser Glu Pro Lys Ser Cys Asp Lys
 260 265 270

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
 275 280 285

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
 290 295 300

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
 305 310 315 320

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
 325 330 335

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
 340 345 350

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
 355 360 365

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
 370 375 380

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
 385 390 395 400

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
 405 410 415

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
 420 425 430

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
 435 440 445

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
 450 455 460

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
 465 470 475 480

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 485 490 495

Lys

<210> 23
 <211> 491
 <212> PRT
 <213> chimera

<400> 23

Met Gln Lys Leu Gln Leu Cys Val Tyr Ile Tyr Leu Phe Met Leu Ile
 1 5 10 15

Val Ala Gly Pro Val Asp Leu Asn Glu Asn Ser Glu Gln Lys Glu Asn
 20 25 30

Val Glu Lys Glu Gly Leu Cys Asn Ala Cys Thr Trp Arg Gln Asn Thr
 35 40 45

Lys Ser Ser Arg Ile Glu Ala Ile Lys Ile Gln Ile Leu Ser Lys Leu
 50 55 60

Arg Leu Glu Thr Ala Pro Asn Ile Ser Lys Asp Val Ile Arg Gln Leu
 65 70 75 80

Leu Pro Lys Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr Asp Val
 85 90 95

Gln Arg Asp Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr His
 100 105 110

Ala Thr Thr Glu Thr Ile Ile Thr Met Pro Thr Glu Ser Asp Phe Leu
115 120 125

Met Gln Val Asp Gly Lys Pro Lys Cys Cys Phe Phe Lys Phe Ser Ser
130 135 140

Lys Ile Gln Tyr Asn Lys Val Val Lys Ala Gln Leu Trp Ile Tyr Leu
145 150 155 160

Arg Pro Val Glu Thr Pro Thr Thr Val Phe Val Gln Ile Leu Arg Leu
165 170 175

Ile Lys Pro Met Lys Asp Gly Thr Arg Tyr Thr Gly Ile Arg Ser Leu
180 185 190

Lys Leu Asp Met Asn Pro Gly Thr Gly Ile Trp Gln Ser Ile Asp Val
195 200 205

Lys Thr Val Leu Gln Asn Trp Leu Lys Gln Pro Glu Ser Asn Leu Gly
210 215 220

Ile Glu Ile Lys Ala Leu Asp Glu Asn Gly His Asp Leu Ala Val Thr
225 230 235 240

Phe Pro Gly Pro Gly Glu Asp Gly Leu Asn Pro Phe Leu Glu Val Lys
245 250 255

Val Thr Asp Thr Pro Lys Arg Ser Asp Lys Thr His Thr Cys Pro Pro
260 265 270

Cys Pro Ala Pro Glu Ala Leu Gly Ala Pro Ser Val Phe Leu Phe Pro
275 280 285

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
290 295 300

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
305 310 315 320

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
325 330 335

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
340 345 350

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
355 360 365

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
370 375 380

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
385 390 395 400

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
405 410 415

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
420 425 430

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
435 440 445

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
450 455 460

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
465 470 475 480

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
485 490